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## THE TREATMENT OF CARDIAC FAILURE WITH DIGITALIS GLYCOSIDES

The intensive search for the active principles of the digitalis group dates back to about the middle of the last century. Large numbers of purified principles have been isolated from the various plants of the digitalis series. Many of the purified materials are mixtures of glycosides rather than single principles. This applies to such preparations as digalen, digifolin, digitan, digilanid, and others. A few represent substantially pure principles.

Qualitatively they all behave alike. Their therapeutic effects are indistinguishable from those of crude digitalis leaf. The indications are that the margin of safety between the amount required to produce the therapeutic effect and the amount which causes a toxic effect does not differ materially from one preparation to another. There are, however, quantitative differences from the pharmacological and clinical standpoints and these pertain to four points: (1) speed of development of action, (2) extent of absorption, (3) duration of action, and (4) potency.

### SPEED OF ACTION

When digitalis glycosides are injected intravenously there is a latent period before the effects on the heart occur. This latent period differs with different materials. It has nothing to do with the matter of absorption since the injection is intravenous. This problem has been studied in a series of patients with heart failure and auricular fibrillation. They were put to bed. The apical rate was counted several times during the day for many days until a constant control level was attained. A dose of a digitalis material was then injected intravenously and the rate counted at intervals of five to ten minutes until the rate declined to the lowest level. The results of such studies, made with ouabain (crystalline strophanthin), cedilanid, digifolin, and digitoxin show that ouabain has the shortest latent period and develops its full effects more quickly than any of the other glycosides. The full effect of ouabain, as measured in this way, is attained in an average period of about two hours, in the case of digitoxin in an average period of about six hours, and between the two fall the curves for the other materials.

### EXTENT OF ABSORPTION

The glycosides of the digitalis series differ in their absorption from the gastro-intestinal tract. The ratio of the oral to the intravenous dose necessary to produce the same effect in patients may be taken as an index of the degree of absorption. This index is somewhat complicated by the factor of elimination, but since the absorption is usually a matter of hours and elimination a matter of days, the major component of the index is the absorption factor, and it serves the practical purpose of revealing how much more of the drug needs to be given by mouth than by vein for similar therapeutic effects.

Several digitalis glycosides have ben studied in this way. The patient with auricular fibrillation and heart failure is put to bed and the apical rate counted in the manner described above. One then determines how much of the drug is necessary in a single dose to produce the same degree of slowing, once by oral administration and at another time by intravenous injection. If the doses are the same, a ratio of 1:1, it may be assumed that the drug is completely absorbed. If, on the other hand, the ratio turns out to be 5:1, it may be taken to indicate that only 20 per cent has been absorbed. The application of this test to several digitalis materials shows that, of a dose of digitalis leaf or of the tincture of digitalis, only about 20 per cent of the active material is absorbed from the gastro-intestinal tract of man, only about 10 per cent in the case of cedilanid, only about 5 to 10 per cent in the case of the glycosides of squills (urginin), about 20 per cent in the case of the purified mixture of glycosides (digifolin), but nearly 100 per cent in the case of the glycoside digitoxin. Complete absorption from the gastro-intestinal tract is a highly desirable property of a digitalis glycoside.

In the case of ouabain (crystalline strophanthin), the absorption from the gastro-intestinal tract of man is so poor that its oral administration is excluded.

Digilanid, a mixture of glycosides from digitalis lanata, has received some attention in the literature. Although strictly comparable tests have not been made, the report by Batterman, Holman and DeGraff indicates that it behaves like crude digitalis with an absorption index of about 5:1 or 20 per cent absorbed.

Digoxin is a pure principle from digitalis lanata which has attracted considerable attention. It is significantly different from digitoxin, with which the name digoxin is often confused. There is some uncertainty concerning the degree of its absorption, and the fact that it is rapidly eliminated may introduce a complicating factor in the determination of the absorption index. A report by DeGraff and Batterman supplies data suggesting that only about 20 per cent is absorbed, although we have a few experiments which indicate that the absorption is higher. It is in need of further study.

### DURATION OF ACTION

In the type of experiments described above, the duration of action of several of digitalis materials was determined. After a full digitalizing dose of the powdered leaves of digitalis, the effects gradually wear off and are virtually completely gone in

a period of from two to three weeks. There are, to be sure, marked individual variations. The duration of action of digitoxin is practically the same as that of the powdered leaves of digitalis. The effects of a full intravenous dose of ouabain wear off in a period of from three to four days. The duration of action of cedilanid and digifolin lies between these two extremes. By this method the exact curve of action of digoxin has not been established but others have found it to be rapidly eliminated, and this is confirmed by some observations in our clinics in which it was found that about 40 per cent of the full digitalizing dose is required daily for maintenance.

## POTENCY

One way of viewing the potency of preparations of digitalis is in terms of the average dose lethal for cats, or the cat unit. Approximately 30 per cent more of the drug converts the value into the U.S.P. unit. For several of the glycosides in common use, the cat unit values are approximately as follows: ouabain, 0.1 mg.; cedilanid, 0.25 mg.; digoxin, 0.28 mg.; urginin, 0.3 mg.; digilanid, 0.33 mg.; digitoxin, 0.4 mg. There are some differences in the values obtained by different workers and for different samples of the same materials. The cat unit, or U.S.P. unit, is of practical importance only in relation to the intravenous injection of the purified glycosides. A fairly high degree of digitalization results from an intravenous dose of 3 to 5 cat units of any of the foregoing materials, with the possible exception of digitoxin which produces about 30 per cent greater effect (for reasons involving a technical problem in assay). The same is true for such mixtures of glycosides as digifolin or digalen or any extract of digitalis.

The cat unit, or U.S.P. unit, is, however, of no practical value as a guide to the clinical potency of the purified glycosides when administered orally. Here variation in absorption vitiates the potency relationships shown by intravenous comparisons. Thus, a daily oral dose of 30 cat units of ouabain produces no effects. The average oral digitalizing dose of many specimens of digitalis leaf is approximately 15 to 20 cat units, of digifolin about the same, of digilanid about 20 cat units (Batterman, Holman, and DeGraff), of cedilanid about 30 to 40 cat units, and of urginin about 40 to 60 cat units. The average digitalizing dose of digoxin is stated as 19.5 cat units (DeGraff and Batterman) although my associates and I have some experiences indicating that this dose is too large. The oral digitalizing dose of digitoxin is only 3 to 4 cat units. Here, then, is a group of purified glycosides of the digitalis group which are used both orally and intravenously, cedilanid, digilanid, digoxin, urginin, and digitoxin; when given intravenously the strongest is less than twice as potent as the weakest, but when administered orally, the strongest is about twelve times as potent as the weakest. As indicated above, absorption accounts for the differences.

## TREATMENT OF CARDIAC FAILURE

The problems of parenteral and oral digitalization may be considered separately. All digitalis glycosides are irritant, much too painful for subcutaneous injection. They may be given intramuscularly, but even in that case pain and tenderness often result. The behavior of the glycosides after intramuscular injection has not been studied sufficiently. Some of our experiences indicate that absorption is irregular and on the average a somewhat larger dose is necessary than by intravenous injection. The choice of preparation for intravenous use is not a matter of great importance. As already stated, an intravenous injection of 3 to 5 cat units (or 2.2 to 3.8 U.S.P. units) of any of the glycosides mentioned above may be counted upon to produce a satisfactory degree of digitalization in the average patient with heart failure who has had little or no digitalis recently (ten days or longer). This dose often will produce the full therapeutic action, although in more tolerant individuals several additional doses of 1 cat unit may need to be given at intervals of four to six hours to complete the effects. Where the matter of an hour or two may be decisive, ouabain is preferable (0.3 to 0.5 mg.) since its full effects are, on the average, developed somewhat more quickly, within two hours in the case of ouabain as against four to six hours for other glycosides of the digitalis group. Individuals are not all the same in this respect and, in some cases, the glycosides may show no substantial difference in speed of action.

The need for intravenous injection of digitalis is infrequent. It should be reserved for some cases of extreme urgency, as in pulmonary edema resulting from acute failure of the left ventricle, or for cases in which, because of coma, vomiting, or other special factors, the oral route is inaccessible.

The rectal route in the case of the purified glycosides has not been studied sufficiently.

For the routine treatment of cardiac failure, the oral is the route of choice, digitoxin (digitaline nativelle) is the glycoside of choice, and digitalization in a single dose the method of choice. Digitoxin is the only glycoside in common use which is practically completely absorbed from the gastro-intestinal tract. A given dose produces as much effect by mouth as by vein. Its duration of action is that of digitalis; so also, its minor toxic effects. The average full digitalizing dose is only 1.2 to 1.5 mg. In the case of most, if not all, the other glycosides in common use, the dose is larger, as much as 6 to 10 mg. of cedilanid and similar or larger doses of urginin for similar therapeutic effects. Such amounts of the glycosides produce sufficient local gastric irritation to induce nausea and vomiting long before any considerable part of the drug is absorbed. The same is true of the 1.2 to 1.5 gram digitalizing dose of digitalis leaf. In order to avoid local gastric upsets, the full dose in these cases is divided into fractions given at intervals of six hours, thereby requiring forty-eight to seventy-two hours to induce the full effects. In the case of digitoxin, on the other hand, an experience with more than 1000 patients indicates that the 1.2 mg. may be safely given at one time. Its full effects develop in from six to ten hours. The 1.2 mg. is the approximate average full digitalizing dose. A cumulative distribution curve of human susceptibility to digitalis has been prepared, which shows that this dose should produce full digitalization in about three-fourths of all cases. In a very small proportion, the effects are more intense than necessary. Minor toxic effects with this dose occur in less than one in fifty cases. A few patients require additional doses of 0.2 mg. at intervals of six hours. The average maintenance dose is 0.2 mg.; in the more susceptible patients, 0.1 mg. daily.

The dose of 1.2 mg. of digitoxin given at one time followed by a daily dose of 0.2 mg. for maintenance has greatly simplified the problem of digitalization in the average patient with cardiac failure. Adjustments in this plan are made for those who have been receiving digitalis. The basis of the adjustment is the fact that digitoxin is 1000 times as potent as the current U.S.P. digitalis by oral administration in man; hence, an allowance of 0.1 mg. of digitoxin for every 0.1 gm. of digitalis.

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